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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/724,530	11/28/00	SIEGALL C	9632-012

020583 HM12/0817
PENNIE AND EDMONDS
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EXAMINER	
CANELLA, K	
ART UNIT	**PAPER NUMBER**
1642	4

DATE MAILED: 08/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/724,530	Slegall et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26, 27, 32-34, and 37* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26, 27, 32-34, and 37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. The restriction requirement of Paper No. 2 is vacated. Applicant's request for the canceling of claims 1-25, 28-31 and 34-36 was overlooked on the transmittal sheet.

2. Claims 26, 27, 32, 33 and 37 are pending and examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 26, 27, 32, 33 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of mice carrying human transplanted lymphoma and myeloma comprising the administration of a protein which increases the binding of CD40 ligand to the CD40 receptor, does not reasonably provide enablement for a method of treating humans carrying tumors arising in situ. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

(A)As drawn to a method of treating tumors arising in situ.

The instant claims encompass the reduction of tumor burden in humans having a naturally occurring tumor in situ. The specification teaches the reduction of tumor burden in mice carrying human myeloma and lymphoma cells after injection with the S2C6 monoclonal antibody which is able to bind to CD40 receptor an enhance the binding of CD40 ligand (T-BAM) to said receptor.. It is known in the art that due to the complexity of the host-tumor immunorelationship, animal models do not fully mimic the biology of the human patient with cancer (G. Ada, Immunology and Cell biology, 1999, Vol. 77, pp. 180-185). Further, immune responses differ between species . For example, Apostolopoulos et al (Nature Med, 1998, Vol. 4, pp. 315-320) have demonstrated a T1 response to mannan Muc1 antigen in mice, but a T2 response to mannan Muc1 antigen in

humans. In addition, the transplanted tumor cells used by the applicant originate from a clonaly derived cell line and are thus homogeneous. Natural tumors arising in situ are often heterogeneous, and the effect of the claimed method upon such a heterogenous tumor has not been demonstrated by the specification. In addition, an effective immunotherapeutic agent must selectively kill tumor cells, not induce anergy to tumor antigen(s) (Becker et al, Int Immunol., 1993, Vol. 5, pp. 1501-1508). However, the specification has not demonstrated selective killing of tumor cells in humans. A tumor specific antigen must be taken up by antigen presenting cells and presented to T-cells in order for the T-cells to become activated against the tumor cells (Carson et al, USP 5,985,847). Human antigen presenting cells must be exposed to a polypeptide at a sufficient concentration and for a sufficient period of time to provoke an efficacious immune response (Matsui et al, J Immunol., 1999, Vol. 163, pp. 184-193). Buhmann et al (Blood, 1999, Vol. 93, pp. 1992-2002) teaches that ligation of the CD40 receptor by binding to CD40 ligand provided on allogenic T-cells allowed for the expansion of specific CD8 CTL against B-cell chronic lymphocytic leukemia cells, whereas autologous T-cells did not induce a relevant CTL response arguing against the applicability of the xenograft model set forth to a method for treating human tumors in situ. Furthermore, it is well known in the art that differential responses to CD40 ligation are exhibited by various lymphomas ranging from apoptosis to expansion (Henriquez et al, Journal of Immunology, 1999, Vol. 162, pp. 3298-3307, Andersen et al, Blood, 1999, Vol. 94, pp. 630a). Given this demonstrated unpredictability in the response of hematopoietic cells expressing CD40 receptor to ligation of said receptor, the response of hematopoietic malignancies in situ to the claimed antibodies could not be predicted. Therefore, one of skill in the art would b subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

(B)As drawn to a method of treating non-CD40 expressing tumors and non-hematopoietic tumors expressing CD40.

The instant claims encompass broadly claimed cancers. The specification suggests that the instant methods encompass CD40 bearing cells that are not B-cells, such as lung carcinoma cells (pg. 38, lines 30-34). The specification further suggests that cells of the malignancy need not

express CD40 since the endothelial cells of the vasculature in proximity to the malignant tumor should express CD40. However, it is known in the art that ligation of CD40 in solid tumors does not result in the same surface phenotype as in hematopoietic cells (Vonderheide et al, Proceedings of the American Association for Cancer Research, 1999, Vol. 40, p. 472), arguing against the existence of a similar mechanism of signal transduction to produce apoptosis or growth stimulation. Furthermore, the specification provides no objective evidence to teach how the induction of apoptosis or any other type of cell death resulting from the suggested, but not substantiated, cross-linking of the putative CD40 receptor on endothelial cells adjacent to a malignant tumor, would result in the diminution of said tumor. Given the lack of teachings regarding the fate of CD40 ligation in non-hematopoietic cells, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed invention.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Patent Examiner, Group 1642
July 1, 2001

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